Amendments to the Drawings:

The attached sheet of drawings includes changes to previous Figure 7, which has been renumbered as Figure 6. This sheet replaces the original sheet including previous Figure 7.

Attachment: Replacement Sheet

REMARKS

Reconsideration of the above-identified application in view of the above amendments and the following remarks is respectfully requested. Claims 1-7, 9-15, 17 and 18 are currently pending. Claims 9-15 are withdrawn from consideration, and claims 1-7, 17, and 18 are currently under examination. By the present amendment, claims 1, 7, and 17 are amended to more specifically recite certain aspects of the invention. Support for these amendments may be found throughout the specification and claims as originally filed and do not constitute new matter. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

Elections/Restrictions

As requested by the Examiner, non-elected claims 9-15 are canceled by the present amendment.

Objection to the Claims

Claim 17 stands objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim for one of the embodiments of the Markush group. Claim 17 has now been amended to remove reference to pre-differentiation of the cells, thereby overcoming this basis of objection. In light of this amendment, Applicants respectfully request that this basis of objection be withdrawn.

Objection to the Drawings

The drawings stand objected to for not containing a Figure 6, in light of the previous cancellation of Figure 6. Applicants submit with this amendment a replacement sheet for previous Figure 7, wherein the figure has been renumbered as Figure 6 to maintain consecutive numbering. In light of this amendment, Applicants respectfully request that this basis of objection be withdrawn.

Objection to the Specification

The specification stands objected to for not containing a brief description of Figure 6, while it contains a brief description of Figure 7. In light of the renumbering of previous Figure 7 such that this figure is now Figure 6, the specification is similarly amended to maintain proper consecutive numbering and refer to the correct figure. In light of this amendment, Applicants respectfully request that this basis of objection be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-7, 17, and 18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More specifically, the Examiner asserts that it is unclear how isolated stromal cells are administered to a patient by the administration of the pre-differentiated isolated stromal cells. In addition, he asserts that the claims are unclear as to the metes and bounds of the pre-differentiation step and also whether the claims are directed to methods of directing differentiation or therapy. The Examiner further indicates that there is insufficient antecedent basis for the term "the brain" in claim 1.

By the present amendment, claim 1 is amended to clarify that the cells administered to the patient are the resulting pre-differentiated isolated stromal cells and to indicate that the brain is that of the patient to whom the cells are being administered. In addition, claim 1 is amended to clarify that the isolated stromal cells are pre-differentiated *in vitro*. Support for this amendment is provided throughout the application as filed, including, *e.g.*, on page 6, lines 24-28, and page 16, lines 2-5, which indicates that cells may be pre-differentiated into a desired phenotype prior to administration to a patient. Additional support for providing such cells to patients is provided, *e.g.*, on page 14, liens 17-21.

Applicants submit that the metes and bounds of the pre-differentiation step are clear in light of the teachings of the instant specification and the knowledge in the art regarding the process of differentiation. The instant specification explains that isolated stromal cells may be pre-differentiated by co-culture with differentiated cells, whereby the stromal cells differentiate and acquire phenotypic characteristics of the differentiated cells (page 6, lines 24-

28). In addition, the instant specification explicitly defines the term "pre-differentiated" to mean isolated stromal cells that are co-cultured with a substantially homogenous population of differentiated cells such that the isolated stromal cells differentiate and acquire phenotypic characteristics of the differentiated cells (page 13, lines 23-26). The specification also explains that it is possible, based upon the data presented within, to pre-differentiate isolated stromal cells to evolve into a desired phenotype prior to their introduction into the central nervous system (page 16, lines 2-5). Based upon these teachings, and in light of the amendment to claim 1, the skilled artisan would clearly understand that the recited pre-differentiation step, which comprises co-culturing the isolated stromal cells with astrocytes *in vitro*, results in the isolated stromal cells differentiating down the astrocyte lineage prior to their administration to the patient. Of course, it is understood that differentiation is a progressive event and that further differentiation may subsequently occur following administration of the pre-differentiated cell to the patient.

Applicants respectfully submit that the claims are now clear and definite and request that the Examiner reconsider and withdraw this basis of rejection in light of the above amendments and remarks.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-7, 17, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, on the basis that the claims contain subject matter not adequately described in the specification and which also constitutes new matter. More specifically, the Examiner asserts that the preamble of claim 1 indicates that pre-differentiation occurs *in vivo*, while the specification states that pre-differentiation occurs *in vitro*. In addition, the Examiner asserts that the instant specification lacks written description support for a method that involves pre-differentiation by co-culture *in vitro*, followed by subsequent differentiation in the human patient following administration of the pre-differentiated cells, which is what he understands the claims to mean in view of the preamble arguably stating that differentiation occurs in the patient.

Applicants respectfully traverse this basis of rejection and submit that the instant claims do not constitute new matter and that the instant specification provides adequate written

description support for the claimed subject matter. As noted above, the claims have been amended to clarify that the cells are pre-differentiated *in vitro* and that the resulting pre-differentiated cells are administered to the patient. In addition, the preamble has been amended to clarify that it is not required that pre-differentiation occurs *in vivo* in the patient. Written description support for the claimed method of providing pre-differentiated cells to a patient is provided throughout the instant specification and claims as filed. For example, support for providing stromal cells to a patient is provided on page 14, lines 17-18, and support for pre-differentiating the cells *in vitro* prior to administration to a patient is provided on page 6, lines 24-28, and page 16, lines 2-5. Specific support for administering isolated stromal cells that have been pre-differentiated into astrocytes is provided, *e.g.*, on page 27, lines 5-7.

Furthermore, support for pre-differentiating the isolated stromal cells by co-culture with astrocytes is also provided. The instant specification teaches that pre-differentiation is performed by "co-culturing stromal cells in the presence of a substantially homogenous population of differentiated cells" (page 6, lines 25-26) and further indicates that astrocytes are differentiated cells (page 15, line 29, to page 16, line 1). While this is clearly sufficient written description support for the recited methods, the specification further describes that the co-cultured differentiated cells used for pre-differentiation may specifically be astrocytes (page 15, lines 28-29) and even exemplifies pre-differentiation performed by co-culturing isolated human stromal cells with astrocytes, demonstrating that a portion of the stromal cells had differentiated into astrocytes (page 53, lines 15-22). The fact that the astrocytes used for co-culture were obtained from rat is irrelevant with respect to written description support for the instant claims. The claims do not require that the astrocytes are obtained from humans, and the skilled artisan would readily appreciate in light of the teachings of the specification that differentiated cells used for co-culture during pre-differentiation could be obtained from an animal other than a rat.

In light of the above amendments and remarks, Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-8, 17, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. More specifically, the Examiner asserts that the claims are directed to methods of treatment and that undue experimentation would be required to practice these claimed methods, given the unpredictability in the art at the time of filing. In particular, the Examiner points out that the instant application is not reasonably predictable to treat any particular disease, and that it would require undue experimentation to determine the amount of cells to administer.

Applicants respectfully traverse this basis of rejection and submit that the presently claimed methods are fully enabled by the instant specification. Applicants submit that the specification, particularly in light of the high level of skill in the art, clearly provides sufficient guidance to enable one of ordinary skill to make and use the entire scope of the instant claims.

Applicants note that the instant claims are directed to a method of providing an isolated stromal cell pre-differentiated into an astrocyte to a human patient suffering from a disease, disorder or condition of the central nervous system. This method is fully described in the instant claims and specification, which recite that the method includes the steps of (1) obtaining a bone marrow sample from a human donor; (2) isolating stromal cells from said bone marrow sample; (3) pre-differentiating said stromal cells by co-culturing them in the presence of astrocytes *in vitro*; and (4) administering the resulting pre-differentiated isolated stromal cells to the central nervous system of said human patient by injection of said pre-differentiated isolated stromal cells into the brain of said human patient. Furthermore, the instant specification provides working examples demonstrating that stromal cells may be readily isolated from bone marrow and differentiated into astrocytes by co-culturing them with astrocytes. For instance, Example 8 demonstrates that human stromal cells isolated from bone marrow can be pre-differentiated into astrocytes by co-culturing them with astrocytes. Example 7 demonstrates that isolated stromal cells may be transplanted into the brains of rats using procedures readily adaptable to humans. Thus, the instant specification clearly enables the skilled artisan to practice the claimed invention.

Nonetheless, the crux of the rejection appears to be that the specification does not enable the use of the claimed methods due to a lack of demonstrated *in vivo* therapeutic efficacy. Although the present claims are directed to a the delivery of differentiated neural cells to a patient suffering from a neurological disease or disorder, the situation is analogous to that described in *In re Brana*, where the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility. 51 F.3d 1560 (Fed. Cir. 1995). The Court even went on to state that "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." *Id.* This is further emphasized in the M.P.E.P., which states that "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention." M.P.E.P. 8th ed. § 2164.02. Thus, it is clearly not required that an application provide working examples of human therapeutic efficacy in order to satisfy the enablement requirement. Rather, the examples described above are sufficient to establish enablement of the claimed method.

To the extent relevant to the instant claims, Applicants would submit that optimizing dosages requires mere routine testing and not undue experimentation. As set forth by the Supreme Court and stated by the Federal Circuit, "[t]he test of enablement is whether one of ordinary skill in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). As repeatedly stated by the Federal Circuit, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), *citing Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), and *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). Indeed, the Court recognized that a considerable amount of experimentation may be required, so long as it does not amount to undue experimentation. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides

a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id., citing In re Jackson*, 217 USPQ 804 (Bd. App. 1982). Clearly, dosage optimization in humans cannot be fully determined until human clinical tests are conducted. However, since such testing is not required to establish enablement, it necessarily follows that human dosages need not be provided to satisfy the enablement requirement.

In view of the above amendments and remarks, and in light of the teaching provided by the instant specification, including working examples demonstrating that the claimed methods work as taught using human cells and in animals, Applicants submit that the claimed invention is sufficiently enabled without requiring undue experimentation. Accordingly, Applicants respectfully request that the Examiner withdraw this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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WTC:jjl

Enclosure:
1 Sheet of Replacement Drawings (Fig. 6)

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